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Isis Pharmaceuticals Inc

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ISIS ANNUAL REPORT 2001

DISMISSING PIPELINE



POWERFUL PARTNERSHIPS



TRANSFORMING YEAR

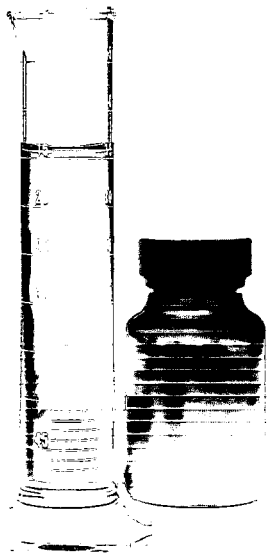


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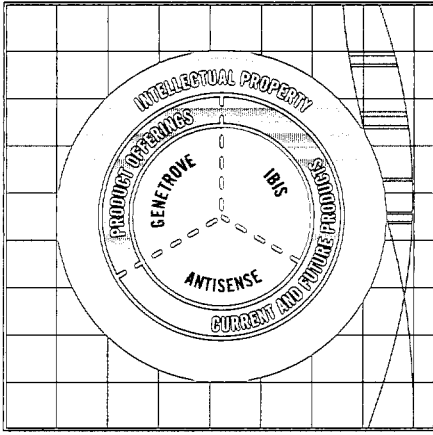


Isis Pharmaceuticals, Inc., is a leading genomics-based drug discovery and development company focused on the untapped therapeutic target, RNA. The goal of the more than 400 people who work at Isis is to develop new medicines that will improve patients' lives.

To reach this goal, we use the technologies we have invented to discover drugs. Our novel approaches also enhance the drug discovery and development productivity of our pharmaceutical company partners.



ISIS' BUSINESS AT-A-GLANCE



A new frontier in drug discovery is at hand. It is based on a novel target, RNA. Isis has pioneered this frontier and is capitalizing on its inventions by developing a broad pipeline of fundamentally new drugs. As demonstrated by the number of important partnerships announced in 2001, the pharmaceutical industry is increasingly excited by the company's revolutionary drug discovery platforms. This in turn has stimulated investor interest in the company.

RNA-BASED DRUG DISCOVERY

Isis has transformed its RNA expertise into four key value drivers:

ANTISENSE RESEARCH AND THERAPEUTICS

Isis is the world leader in antisense technology. Through advances in basic antisense research, medicinal chemistry, and molecular and cellular biology, the company's scientists have created a new class of drugs. Based on gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. Isis has a total of 13 antisense products in its development pipeline, with two in Phase III and six in Phase II programs. These drugs are being studied in multiple formulations for the treatment of a broad range of diseases.

GENETROVE™ GeneTrove, the functional genomics division of Isis, exploits the specificity

of antisense to provide functional genomics data to pharmaceutical companies and generate revenue for Isis. GeneTrove can rapidly identify what a gene does (gene functionalization) and whether a specific gene is a good target for drug discovery (target validation), with the goal of improving partners' drug discovery decisions. GeneTrove's product offerings include Custom Target Validation collaborations, access to its Human Gene Function Database and Antisense Inhibitor Library, and licenses to its functional genomics patent portfolio.

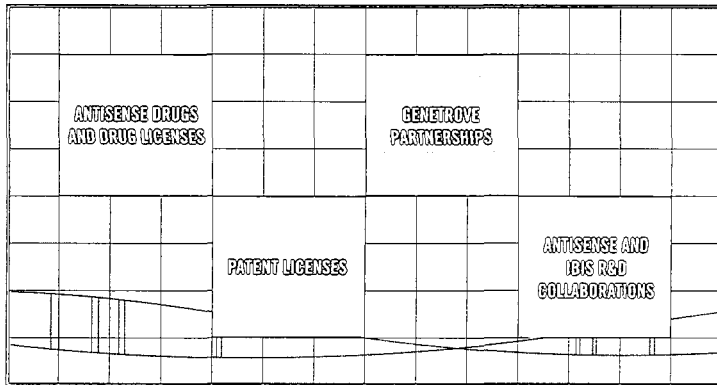
IBIS THERAPEUTICS™ Ibis Therapeutics has developed technology to revolutionize the detection and treatment of infectious diseases. Ibis seeks to discover small molecule drugs that work by binding to RNA targets implicated in disease processes. This

program has been funded by a pharmaceutical partnership and by grants from the U.S. Department of Defense. The government's interest lies with the technology's potential value in biological warfare defense.

INTELLECTUAL PROPERTY With rights to more than 900 issued patents, Isis holds the largest RNA-based patent estate in the pharmaceutical industry. This estate is a product of 13 years of research innovation. The company has established an active enforcement and licensing program to protect its inventions, aid partners in developing new therapies for patients and generate revenue. Isis' intellectual property includes patents covering antisense mechanisms, chemistries, manufacturing, functional genomics processes and inhibitors to hundreds of genes, as well as inventions covering Ibis' technology.



ISIS' MULTIPLE SOURCES OF REVENUE



DEAR STOCKHOLDERS

2001 was a pivotal year for Isis. Antisense technology has been reexamined by the pharmaceutical industry as well as by Wall Street. Each of these audiences has become increasingly interested in antisense, and Isis is recognized as the pioneer and leader of this technology.

During the year, we made great progress scientifically, in the advancement of our large product pipeline, and in our business development efforts. Our broad, strategic drug discovery and development relationship with Eli Lilly and Company was clearly the most significant transaction of the year. We are proud of our accomplishments, and this annual report catalogs the year's major events and our plans moving forward.

"THE SUCCESS WE ENJOYED IN 2001 WAS THE PRODUCT OF 13 YEARS OF SCIENTIFIC PROGRESS AND THE EXECUTION OF OUR BUSINESS PLAN."



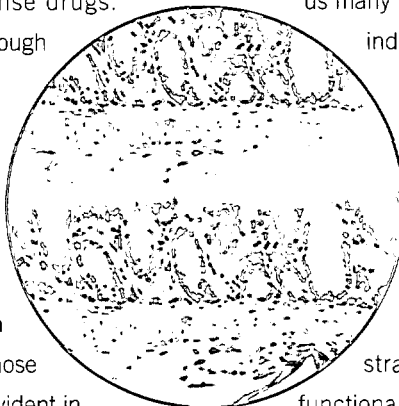
STANLEY T. CROOKE, M.D., PH.D.
ISIS CHAIRMAN AND CEO

Our business plan is to generate value in several ways:

CONTINUE TO CREATE A STREAM OF RNA-BASED DRUGS. The journey we began in 1989 started with a carefully constructed drug discovery strategy that enabled us to learn, step by step, about the technology and the properties of antisense drugs.

Our drug discovery strategy has advanced through several stages:

- First, when the technology was very new, we designed antisense drugs to treat local diseases—those limited to a defined area. We accomplished this through the commercialization of Vitravene®.
- Then, as we learned more about the technology and the properties of antisense drugs, we began designing drugs for severe systemic diseases—those that occur throughout the body. Our progress is evident in the late-stage clinical programs for LY900003 (ISIS 3521) in cancer and alicaforsen (ISIS 2302) in Crohn's disease.
- Now, we are exploiting what we have learned and the improvements we have made to design drugs to treat chronic diseases in which patient convenience is required. As part of this progress, we have



of antisense drugs and the efficiency of antisense drug discovery and development. We hope to enjoy a similar scope of opportunity with our Ibis Therapeutics™ drug discovery technology. To enhance value and offset clinical risk, we are developing multiple products, giving us many shots on goal, and are sharing expense and risk with industry partners. With our large product pipeline, and drug discovery collaborations with Lilly, Amgen Inc., the Department of Defense and others, we are well along in the implementation of this plan.

CONTINUE TO ENHANCE ANTISENSE DRUG DISCOVERY THROUGH GENETROVE PARTNERSHIPS.

Our GeneTrove™ division generates revenues and strategic advantage for Isis. Our partners pay us to functionalize genes, generally on a non-exclusive basis, and we keep rights to antisense drugs discovered through these activities. Over the next three years, we expect our current collaborations to fund the functionalization of more than 1,400 genes. GeneTrove has two additional means of generating near-term revenue: sales of its Human Gene Function Database and Antisense Inhibitor

POSITIVE RESULTS FROM FIRST STUDY OF SECOND-GENERATION ANTISENSE DRUGS IN HUMANS

STRATEGIC ALLIANCE WITH ELI LILLY AND COMPANY

created improved antisense chemistries that greatly enhance the potency, stability and safety of these drugs. The initiation of clinical trials of ISIS 104838 in rheumatoid arthritis and the recent addition of four new drugs to our pipeline are examples of progress with our proprietary second-generation chemistry.

Our research success has led to the creation of an exciting pipeline of 13 antisense products.

Data demonstrate that antisense drugs can be applied to broad therapeutic areas and delivered by a wide variety of routes: injection, inhalation, enema, topical cream, and we hope soon to be achieved, oral. With this knowledge and our leadership position in the technology, we are exploiting the business opportunities at hand.

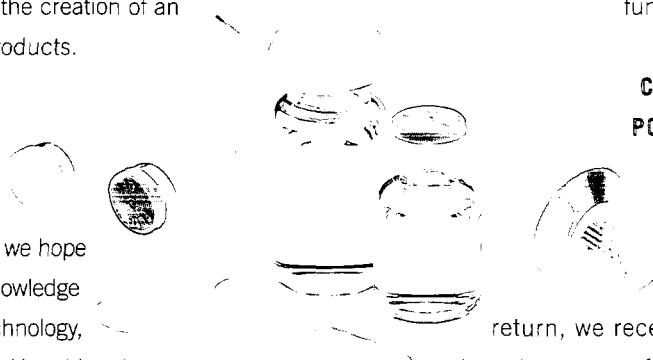
We plan to discover more antisense drugs than we can afford to fully develop on our own, advance the drugs to value inflection points, then partner most drugs and participate significantly in the economics of their commercialization. We believe this approach is feasible because of the broad therapeutic potential

Library, and licenses to antisense-based functional genomics intellectual property. As part of several new GeneTrove partnerships, we have licensed rights to functionalize genes using our patented antisense mechanisms to Amgen, Chiron Corporation, and Pharmacia Corporation for use in their respective in-house functional genomics programs.

CONTINUE TO EXPLOIT OUR LEADERSHIP POSITION IN ANTISENSE TECHNOLOGY.

We plan to selectively extend our expertise and intellectual property to industry partners who seek to develop antisense therapeutics. In return, we receive an ownership interest in a much broader range of antisense drugs and/or companies.

This provides Isis the opportunity to create a broader antisense pipeline than we could otherwise develop, while reducing risk to the company. We have been successful with this plan, as demonstrated by our partnerships with OncoGenex Technologies Inc., Antisense Therapeutics Limited and major



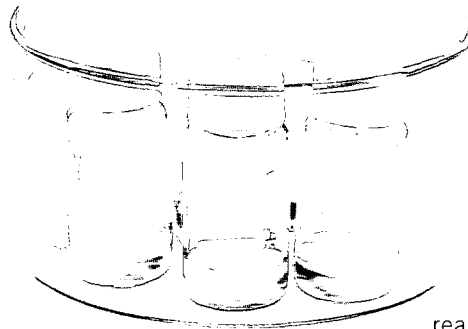
pharmaceutical companies. We believe Isis will have more opportunities to make similar transactions. Combined with the ongoing development of our own antisense drug pipeline, we believe such partnerships will enable us to participate fully in establishing a new sector of the pharmaceutical industry based on antisense technology.

Through our Ibis division, we have another opportunity to bring value to Isis and the industry. Ibis has made steady progress toward the discovery of small molecule drugs that bind to structured areas of RNA, using its proprietary technology. We have also created a new application of Ibis' technology that may provide an opportunity to revolutionize the field of anti-infective diagnostics.

We are very pleased with the progress made in executing our business plan in 2001. We have advanced our technology through focus, innovation and persistence. We have an expanding roster of strong partners who are enthusiastic about the opportunity to create new RNA-based drugs.

We are also focused on strengthening our business. In 2002 our goals are to:

- Advance our current partnerships toward success milestones
- Initiate new GeneTrove partnerships
- Initiate at least one additional antisense drug discovery partnership
- Expand, defend and exploit our intellectual property position to protect our inventions, attract partners and generate revenue.



WE HAVE A CLEAR AGENDA FOR 2002, AND MANY OPPORTUNITIES TO CREATE VALUE IN THE COMING YEARS. Our scientific and business accomplishments in 2001 support our belief that we are on the path to realizing our vision and establishing antisense as

a revolutionary platform for drug discovery. We are pleased to continue our journey from a position of unprecedented strength. We recognize that we still have substantial work ahead and that we, like all companies engaged in drug discovery, are likely to encounter unexpected challenges. We have learned from our progress

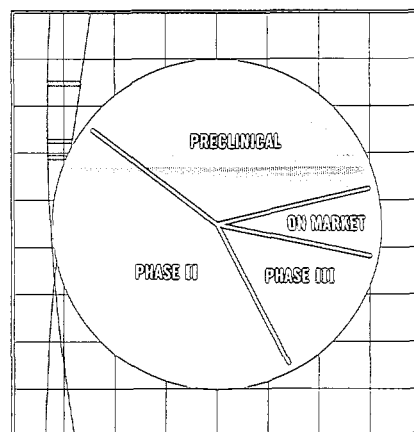
VALUE GENERATION FROM INTELLECTUAL PROPERTY POSITION

SUCCESS OF GENETROVE DIVISION

TO THAT END, WE ARE ENGAGED IN AN ABUNDANCE OF DRUG DEVELOPMENT ACTIVITY IN 2002. Already, we have completed enrollment of 600 patients with non-small cell lung cancer (NSCLC) in a Phase III trial of LY900003 (ISIS 3521). Additional research and development goals for 2002 are as follows:

- Advance clinical development of multiple products through
 - continued progress of our two Phase III trials, in NSCLC and Crohn's disease, and six Phase II programs
 - expansion of our Phase II programs
 - initiation of a Phase I trial for at least one additional drug candidate
- Advance development of oral formulations for antisense drugs
- Advance antisense technology and drug discovery into new therapeutic areas
- Advance the Ibis drug discovery and diagnostic programs.

ISIS' DEVELOPMENT PIPELINE



and we are enthusiastic about our opportunities. We are financially strong. We have a dedicated and experienced management team with a rich history of successfully developing and commercializing drugs. We have leadership positions in exciting new technologies and an intellectual property position sufficient to greatly influence,

or even control, their development. We are united in important common purposes: to help patients and return value to our stockholders. We welcome and appreciate your support along the way.

Sincerely,

STANLEY T. CROOKE, M.D., PH.D.

Chairman and Chief Executive Officer

*"ISIS IS IN THE STRONGEST
FINANCIAL POSITION IN THE
COMPANY'S HISTORY."*



B. LYNNE PARSHALL, J.D.
ISIS EXECUTIVE VICE PRESIDENT AND
CHIEF FINANCIAL OFFICER

The visibility of Isis' scientific progress reached new heights primarily through a series of exciting partnerships in 2001. These collaborations enhanced appreciation of the potential value of antisense technology and of Isis' status in the field. The broad strategic relationship established with Eli Lilly and Company and the fortified financial position that resulted from the company's cumulative business development and financing successes were the two most important business accomplishments of the year.

EXECUTION OF 2001 COMPANY GOALS AND BUSINESS STRATEGY

POSITIVE CLINICAL DATA

NEW ANTISENSE THERAPEUTICS PARTNERSHIPS WITH SECTOR LEADERS

RECORD REVENUES AND SUCCESSFUL SECONDARY OFFERING



ISIS' PARTNERSHIPS

ISIS DRUG DISCOVERY	ANTISENSE DRUG DEVELOPMENT	GENETROVE™	ISIS THERAPEUTICS™	PATENT LICENSES
AMGEN ANTISENSE THERAPEUTICS LTD. ELI LILLY AND COMPANY MERCK & CO.	ANTISENSE THERAPEUTICS LTD. ELAN-HEPASENSE™ ELAN-DRASENSE™ ELI LILLY AND COMPANY MERCK & CO. ONCOGENEX TECHNOLOGIES ANTISENSE COMMERCIALIZATION NOVARTIS OPHTHALMICS	ABBOTT LABORATORIES AMGEN AVENTIS CELERA GENOMICS CHIRON CORPORATION ELI LILLY AND COMPANY JOHNSON & JOHNSON MERCK & CO. PHARMACIA CORPORATION	AGOURON PHARMACEUTICALS (A PFIZER COMPANY) DARPA-DIAGNOSTICS DARPA-DRUG DISCOVERY USAMRIID	EYETECH PHARMACEUTICALS HYBRIDON PANTHECO A/S ROCHE DIAGNOSTICS

PARTNERS LISTED IN ALPHABETICAL ORDER

BUSINESS ACCOMPLISHMENTS

The relationship with Lilly is a transforming event for Isis as it involves all aspects of the company's antisense business. Lilly licensed LY900003 (ISIS 3521), Isis' anticancer drug that is in Phase III trials in patients with non-small cell lung cancer. The companies also initiated a four-year drug discovery collaboration, in which Isis and Lilly will identify the function of up to 1,000 genes through Isis' GeneTrove division. In addition, the companies will work together to discover antisense drugs to treat inflammatory and metabolic diseases.

THE LILLY COLLABORATION IS OF STRATEGIC IMPORTANCE TO ISIS FOR SEVERAL REASONS:

- It enhances the commercial potential of LY900003 (ISIS 3521). Lilly is capable of greater investment in the drug's development and is ideally positioned to commercialize LY900003 (ISIS 3521).
- It acknowledges the potential of antisense technology to make novel drugs for diseases with significant therapeutic needs.

- It is a strong vote of confidence in the strength of GeneTrove's functional genomics program.
- It has fortified Isis' financial position. Lilly has committed more than \$200 million to Isis in this broad drug discovery and development alliance. Assuming the success of LY900003 (ISIS 3521) and of multiple drugs from the research collaboration, Isis has the potential to earn contingent funds in excess of \$200 million over the life of the drugs' development. Isis also has the opportunity to earn royalties on sales of drugs resulting from the partnership. Isis' business model provides the company with an opportunity to generate revenue and cash from multiple sources, in addition to major corporate partner arrangements such as that with Lilly.

IN 2001, ISIS BENEFITED FINANCIALLY FROM SUCCESS IN EVERY AREA OF ITS BUSINESS.

As a result, the company's financial position at year-end was the strongest in Isis' history.

Aided by the completion of 17 transactions with 13 pharmaceutical and biotechnology

companies, Isis generated record revenue of \$53 million. This revenue resulted from licensing antisense drugs, initiating antisense drug discovery partnerships, establishing new GeneTrove collaborations, licensing intellectual property, achieving milestones, and making progress in existing partnerships. In total, revenue increased 43% over the previous year. Importantly, this funding enabled Isis to make continued progress in its very broad research and clinical agenda while reporting a net operating loss in line with company and investor expectations.

Isis' business activities and the completion of a public offering of common stock substantially strengthened the company's balance sheet. Isis ended the year with a cash balance of more than \$300 million. Combining current cash with cash committed over the next four years from existing partnerships, Isis expects to have nearly \$450 million available to pursue its programs.

The business and financial accomplishments of 2001 have enhanced the company's opportunity for continued success.

ISIS' PRODUCT PIPELINE

PRODUCT (FORM)	TARGET	LEAD INDICATION	PARTNER	PRECLINICAL	PHASE I	PHASE II	PHASE III	ON MARKET
VITRAVENE (I)	ANTIVIRAL	CMV RETINITIS	NOVARTIS					
LY900003 (ISIS 3521) (P)	PKC- α	CANCER - NSCLC, OTHERS	LILLY					
ALICAFORSEN (ISIS 2302) (P)	ICAM-1	CROHN'S DISEASE	ISIS					
ALICAFORSEN (ISIS 2302) (T)	ICAM-1	PSORIASIS, OTHERS	ISIS					
ALICAFORSEN (ISIS 2302) (E)	ICAM-1	ULCERATIVE COLITIS	ISIS					
ISIS 14803 (P)	ANTIVIRAL	HEPATITIS C	ELAN					
ISIS 2503 (P)	H-RAS	CANCER - PANCREATIC, OTHERS	ISIS					
ISIS 1C4838 (P,O)	TNF- α	RHEUMATOID ARTHRITIS	ISIS/ELAN					
ISIS 104838 (T)	TNF- α	PSORIASIS	ISIS					
ISIS 113715 (P)	PTP-1B	DIABETES	MERCK					
ISIS 13650 (I)	C-RAF	DIABETIC RETINOPATHY, OTHERS	ISIS					
ISIS 107248 (P)	VLA-4	MULTIPLE SCLEROSIS, OTHERS	ATL					
OGX-011 (P)	CLUSTERIN	CANCER - PROSTATE, OTHERS	ONCOGENEX					
ISIS 23722 (P)	SURVIVIN	CANCER	ISIS					
I=INTRAVITREAL	P=PARENTERAL	E=ENEMA	T=TOPICAL	O=ORAL	○ FIRST-GENERATION CHEMISTRY	○ SECOND-GENERATION CHEMISTRY		

PIPELINE PROGRESS

"WITH OUR EXTENSIVE ANTI-SENSE PIPELINE, WE HAVE THE POTENTIAL TO SUBSTANTIALLY IMPROVE PATIENTS' HEALTH."



F. ANDREW DORR, M.D.
ISIS VICE PRESIDENT AND
CHIEF MEDICAL OFFICER

ISIS' PIPELINE IS THE COMPANY'S MOST VALUABLE ASSET. Based on expertise gained from more than a decade of core antisense research, Isis scientists have created the largest antisense pipeline, comprised of 13 drugs. This pipeline provides the company with multiple opportunities to improve the health of millions of people through a fundamentally new class of drugs, to enter into strategic corporate transactions, and to generate value for shareholders.

2001 was an unprecedented year for Isis in the development of its drug pipeline. The company presented compelling preclinical data on its first Type 2 diabetes drug, now licensed to Merck & Co., Inc. Clinically, Isis initiated several trials and reported positive data on five antisense drug products, tested in both acute and chronic diseases.

CLINICAL DATA HIGHLIGHTS OF 2001 AND NEXT STEPS:

- **LY900003 (ISIS 3521)** Isis reported an increase in the survival of people with non-small cell lung cancer in a combination Phase II trial of LY900003 (ISIS 3521), an antisense inhibitor of protein kinase c-alpha (PKC- α). Eli Lilly and Company is planning to explore LY900003 (ISIS 3521) in multiple cancer indications and with other chemotherapy regimens. The drug will benefit from Lilly's leadership position in the oncology market and its worldwide commercialization capabilities. Early in 2002, Isis and Lilly announced completion of enrollment of the ongoing 600-patient Phase III clinical trial of LY900003 (ISIS 3521) in non-small cell lung cancer. Depending on the strength of the results of the first Phase III trial, Isis and Lilly plan to file a new drug application with the FDA in either 2003 with a single study, or in 2004 with a two-study application.

◦ **ALICAFORSEN (ISIS 2302) INTRAVENOUS**

The company initiated a 150-patient Phase III trial of alicaforsen (ISIS 2302), an antisense drug that inhibits Intercellular Adhesion Molecule-1 (ICAM-1), in people with active Crohn's disease. This study will evaluate the safety and efficacy of alicaforsen (ISIS 2302) at doses higher than previously studied in controlled trials. Isis plans to begin a second, similar Phase III trial in Europe in 2002.

◦ **ALICAFORSEN (ISIS 2302) TOPICAL**

Isis reported that topical alicaforsen (ISIS 2302) penetrated human psoriatic lesions and was active in a Phase II clinical trial in people with psoriasis. More recently, a second Phase II trial confirmed and extended these results. The company is considering further development of this drug in combination with other medications for psoriasis or as a single agent in additional skin diseases.

◦ **ALICAFORSEN (ISIS 2302) ENEMA**

The company reported statistically significant reduction in disease activity index in people with active distal ulcerative colitis in a Phase II study of alicaforsen (ISIS 2302) administered by enema. In 2002, Isis plans to compare alicaforsen (ISIS 2302) enema to an existing ulcerative colitis treatment in a Phase II trial.

◦ **ISIS 14803 HepaSense™**, a joint venture

between Isis and Elan Corporation, plc., reported reduction of viral load in a small Phase I/II study of ISIS 14803 in people with drug-resistant, chronic Hepatitis C Virus. A Phase II trial studying longer-term dosing began in early 2002, and an additional study of ISIS 14803 in combination with current therapies is planned.

◦ **ISIS 104838**

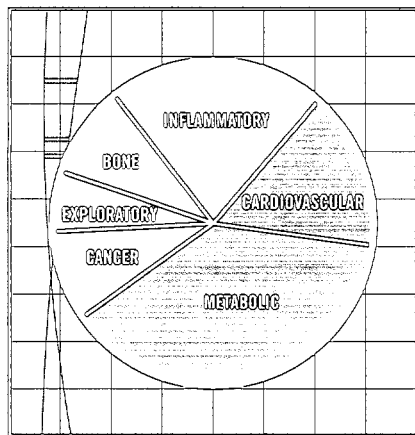
Isis reported improved dosing frequency and safety of

second-generation chemistry in a Phase I study of ISIS 104838, an antisense inhibitor of tumor necrosis factor-alpha (TNF- α), and the first of Isis' second-generation antisense drugs to be tested in humans. Phase II trials of ISIS 104838 are ongoing in people with rheumatoid arthritis, and in people with psoriasis, where Isis is studying a topical formulation.

The products in Isis' pipeline address areas of significant unmet medical need. The company is committed to the aggressive development of its drugs in order to benefit patients and shareholders.



THERAPEUTIC AREAS OF ANTISENSE RESEARCH



Antisense drugs are small DNA-like molecules designed to work by using genetic information directly to prevent the production of specific disease-causing proteins. By contrast, conventional drugs bind to disease-causing proteins that have already been produced. Due to exquisite specificity, antisense drugs may have enhanced therapeutic effects without the undesirable side effects of conventional therapy.

RESEARCH ADVANCEMENT

"BY TARGETING RNA, WE CAN PURSUE THERAPEUTIC OPPORTUNITIES THAT HAVE BEEN DIFFICULT TO ADDRESS THROUGH OTHER PLATFORMS."



C. FRANK BENNETT, PH.D.
ISIS VICE PRESIDENT, ANTISENSE RESEARCH

Isis' success in pioneering antisense technology has resulted in second-generation antisense drugs with increased potency and stability, an improved side effect profile and the potential for oral bioavailability. Coupled with advances in new formulations (oral, topical cream, intravenous, subcutaneous, intravitreal, aerosol, and enema), Isis' investment in core antisense research has produced a rich pipeline based on a novel, potentially broadly useful class of drugs.

An important research goal in 2002 is the creation of an oral formulation platform for antisense drugs. Through the company's joint venture with Elan Corporation, plc., called Orasense™, Isis is making progress toward this milestone. Orasense is currently evaluating oral formulations in humans to identify the most advantageous form to advance into clinical studies. ISIS 104838, a second-generation antisense drug that

inhibits tumor necrosis factor-alpha (TNF- α), is the antisense drug Orasense is using as a prototype. If oral delivery is achieved, the convenience gained will allow Isis to pursue drugs for a much broader range of diseases.

As with the development of any new drug discovery technology, Isis' understanding of antisense has steadily improved with experience. Isis scientists have gained insight into the capabilities of antisense drugs and their behavior in the body, including to which organs antisense therapy is best directed. Isis' research strategy leverages this knowledge and focuses the company's resources towards therapeutic areas of greatest potential. Isis has already enjoyed significant progress in areas such as oncology as well as inflammatory and metabolic diseases. The company is rapidly expanding one of its newest and most

exciting programs, metabolic diseases research.

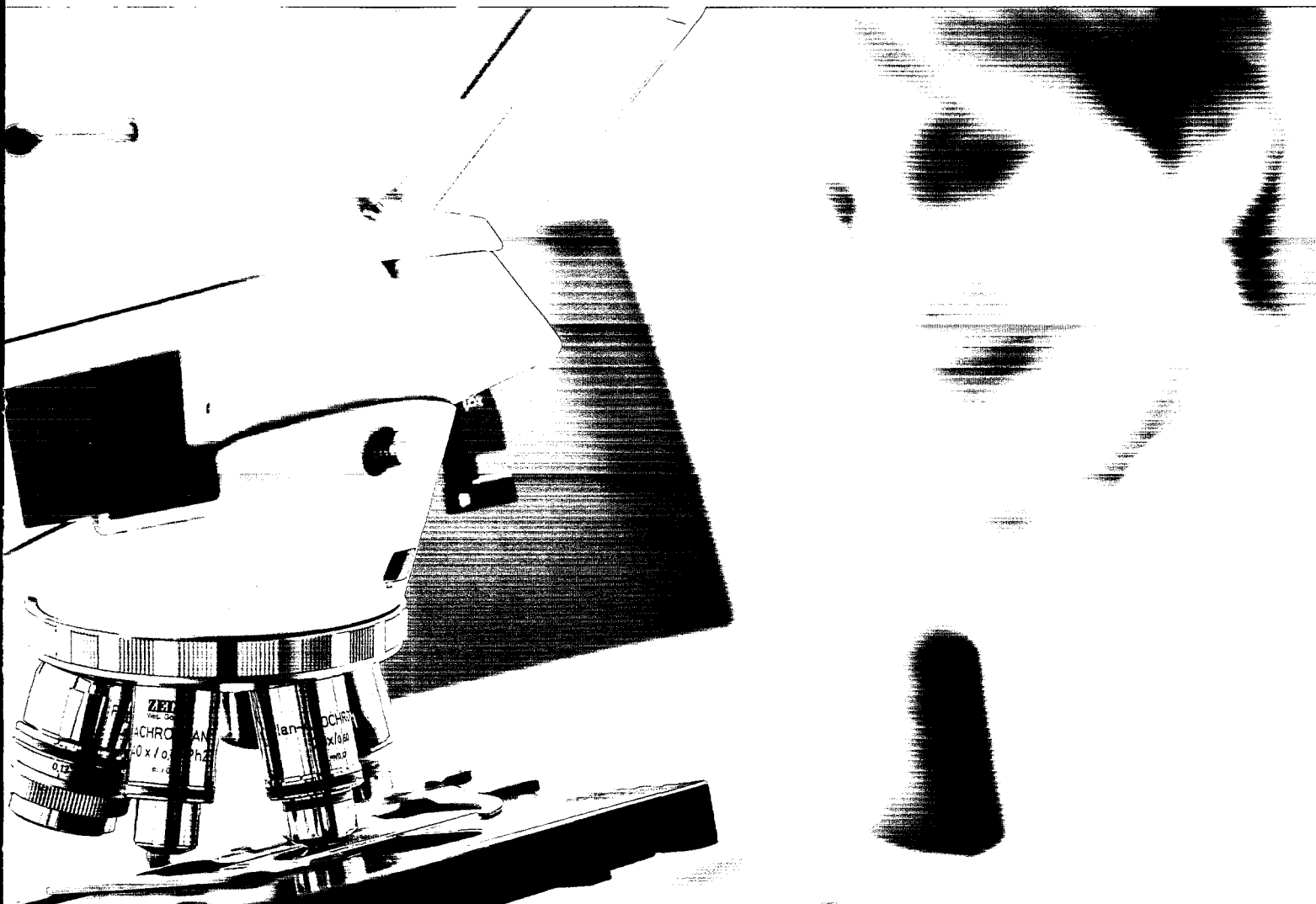
In the past 18 months, the Isis research team has produced four new second-generation antisense drugs for Isis' product pipeline: ISIS 113715 for Type 2 diabetes, OGX-011 for prostate cancer, ISIS 13650 for diabetic retinopathy and age-related macular degeneration and ISIS 23722 for cancer.

Isis continues to focus its research on organs and tissues that readily accumulate antisense drugs. Isis scientists are exploring the antisense opportunity of the liver, kidney, fat tissue and bone marrow. These targets expand the current therapeutic scope of research into new disease categories, including obesity and cardiovascular disease.

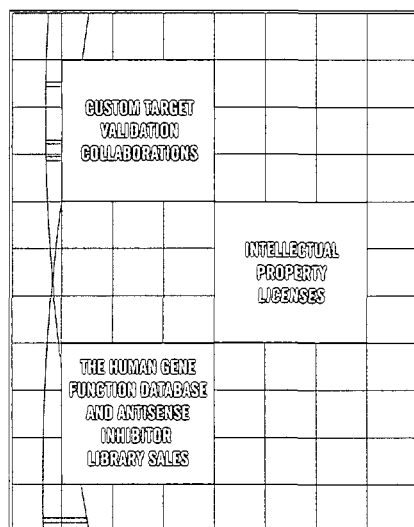
Isis researchers also pursue molecular targets considered 'undruggable' by traditional drug discovery methods. Traditional drugs bind to proteins, and due to the way they bind, can only target a small fraction of disease-causing proteins. Antisense drugs, in contrast, use RNA sequence information as a highly specific basis for binding to their targets. Therefore, nearly all drug targets are approachable, as antisense drugs work at the RNA level to inhibit the production of disease-causing proteins. The improved specificity of antisense drugs allow them to be more effective and less toxic than traditional drugs.

Data Isis has generated during 13 years of research have supported the

initiation of important antisense drug discovery relationships with industry leader Eli Lilly and Company in the areas of metabolic and inflammatory diseases, and most recently, Amgen Inc. Isis also works with hundreds of academic institutions and top researchers worldwide to further the basic understanding of antisense technology, its applications as a therapeutic platform and as a functional genomics research tool. The company is optimistic that as its science continues to advance, industry interest will continue to broaden.



GENETROVE'S PRODUCT OFFERINGS



With the mapping of the human genome, the pharmaceutical industry is faced with the task of sorting through large amounts of genomic data to gain insight into the biological role of individual genes. Drug discovery companies require access to accurate information to make crucial resource allocation decisions for their drug discovery and development programs. Isis is capitalizing on the utility of antisense as a genomics tool through its GeneTrove™ division.

GeneTrove offers antisense-based functional genomics solutions to partners.



GENETROVE OPPORTUNITY

**"GENETROVE PROVIDES
RAPID AND EFFICIENT
ANSWERS TO THE INDUSTRY'S
GENOMIC QUESTIONS."**



RICHARD K. BROWN, PH.D.
ISIS VICE PRESIDENT AND
GENETROVE PRESIDENT

GeneTrove leverages Isis' antisense expertise to actively expand the company's drug discovery program, generate revenue and enhance industry acceptance of antisense. Through three product offerings, GeneTrove assists partners with the challenges of drug discovery, and creates strategic advantage for Isis.

CUSTOM TARGET VALIDATION

COLLABORATIONS. In these partnerships, Isis' customers pay the company to functionalize genes, generally on a non-exclusive basis. Isis keeps rights to antisense drugs discovered in the process. This past year, GeneTrove initiated new Custom Target Validation partnerships with Celera Genomics, Eli Lilly and Company, Chiron Corporation, Amgen Inc., and, most recently, Merck & Co., Inc. and Pharmacia Corporation.

An early example of antisense target

validation success is the combined efforts of a GeneTrove collaborator and Isis' drug discovery group, which produced a compelling data package for a preclinical antisense drug directed to the diabetes target PTP-1B. In the process, Isis researchers identified potent inhibitors to nearly 20 interesting insulin-signaling targets and tested the effects of their inhibition in cell and animal models. The antisense inhibitor of PTP-1B emerged from these experiments as an interesting drug candidate and was licensed to Merck in 2001.

HUMAN GENE FUNCTION DATABASE AND ANTISENSE INHIBITOR LIBRARY.

GeneTrove is working to define the function of up to 10,000 human genes, and will organize and sell this data in its subscription database. Content will be derived from pharmacological tests conducted in *in vitro* models of

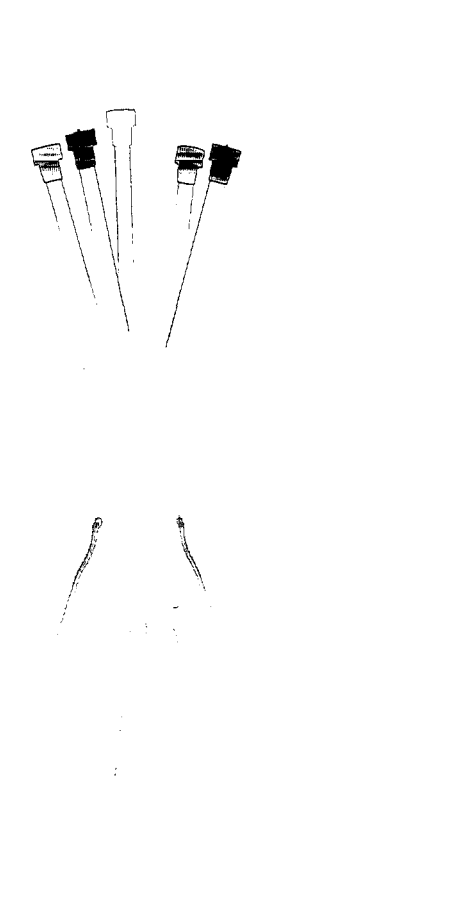
oncology, angiogenesis, inflammation and metabolism. GeneTrove's proprietary software allows researchers to query the database's high-quality gene function data and gain unique insight on the role of genes in disease processes.

INTELLECTUAL PROPERTY LICENSING

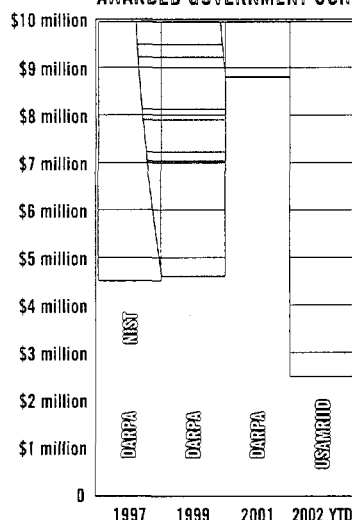
PROGRAM. GeneTrove leverages Isis' patent estate to encourage the industry to collaborate for antisense-based functional genomics activities. Isis' functional genomics intellectual property suite is comprised of more than 50 issued patents in areas such as antisense mechanisms of action, antisense inhibitor designs and chemistries. Isis encourages pharmaceutical companies that prefer to perform antisense-based functional genomics experiments independently to license access to those patents with-

in Isis' intellectual property estate that pertain to their activities. As part of target validation collaborations with GeneTrove, Chiron, Amgen and Pharmacia have taken licenses to specific patents within this suite to perform antisense-based target validation in their respective in-house functional genomics programs.

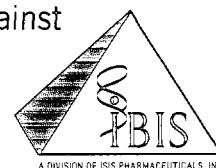
GeneTrove partnerships open the door for new industry relationships. As collaborators use antisense technology for functional genomics, they have an opportunity to experience its utility and value. Their experience with GeneTrove may lead to an increased interest in antisense technology for therapeutics, providing Isis with additional partnering opportunities.



AWARDED GOVERNMENT CONTRACTS



Ibis Therapeutics™ is capitalizing on the investment Isis has made in understanding RNA as a novel site for drug discovery. The division has created proprietary technology to design small molecule drugs that bind to structured regions of RNA—areas of RNA that are less attractive for antisense drug discovery. There are three major components to Ibis' technology: RNA target identification, revolutionary high-throughput technology to screen against structured RNA targets based upon mass spectrometry, and new chemical structures that bind to RNA.



Ibis has initially focused on the discovery of anti-infective drugs. This past year the division expanded its program to include a diagnostic application of its technology. The Defense Advanced Research Projects Agency (DARPA) awarded Ibis a contract in 2001 for up to \$8.9 million to create a revolutionary biological sensor. DARPA is a government agency with research programs focused on the defense against potential biological attacks. The diagnostic device will be designed to rapidly detect all biological threat agents including bacteria, viruses, fungi and parasites, as well as unknown, newly emergent, or genetically modified organisms. Ibis' novel approach does not require culturing of organisms. The research program, entitled Triangulation Identification Genetic Evaluation of biological Risks (TIGER), combines Ibis' expertise in microbial genome sequence analysis and advanced mass

***"WE BELIEVE IBIS' TECHNOLOGY
CAN REVOLUTIONIZE ANTI-
INFECTIVE DRUG DISCOVERY
AND DIAGNOSTICS."***



**DAVID J. ECKER, PH.D.
ISIS VICE PRESIDENT AND
IBIS THERAPEUTICS PRESIDENT**

factors also support Ibis as a technology uniquely suited for the problem of bio-warfare defense. Ibis' work for DARPA has yielded a number of proprietary targets and significant advances in RNA-targeted drug design. In 2002, Ibis successfully transitioned this therapeutics program to the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Combined with Ibis' diagnostic award, the division has received government-funded contracts totaling more than \$20 million.

In 2001, Ibis continued its relationship with Agouron Pharmaceuticals, Inc., a Pfizer company, to identify novel RNA targets and screen small molecules for the discovery and development of new drugs. Ibis' progress in this collaboration in 2001 was reflected in the achievement of two milestones totaling \$4 million.

IBIS INNOVATION

spectrometry technology with the signal processing capabilities of San Diego-based Science Applications International Corporation (SAIC). Ibis' goal is to apply this invention to both biowarfare defense and commercial healthcare opportunities.

This new partnership builds on Ibis' existing relationship with DARPA to discover broad-spectrum anti-infective drugs to combat biowarfare threats. Research conducted since 1997 has focused on creating a strategy to identify common binding sites, or structured regions within RNA, in a wide range of infectious agents. Ibis then uses these sites as targets for binding small molecule drugs to fight infectious pathogens. The universal nature of RNA, and the fact that there are sites in RNA that are the same across all infectious organisms, serve as the basis for Ibis' quest to make broad-spectrum anti-infective drugs. These

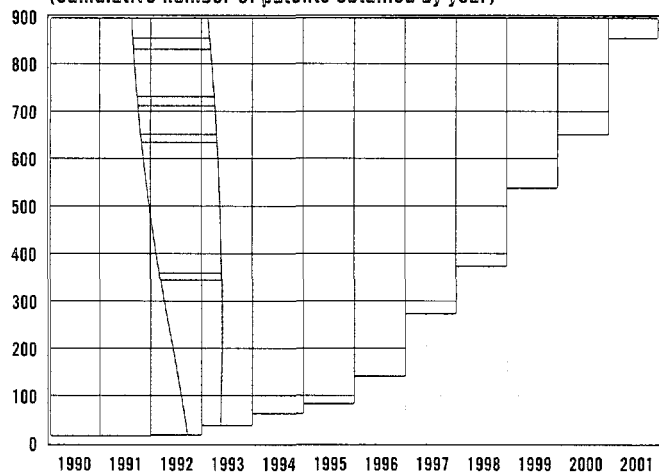
***"ISIS' NOVEL BIOINFORMATICS
TECHNOLOGIES ENHANCE
THE QUALITY AND SPEED OF
DRUG DISCOVERY."***



**JOHN MCNEIL
ISIS VICE PRESIDENT, INFORMATICS**

The Ibis technology platform integrates comparative functional genomics, proprietary bioinformatics algorithms and an RNA-focused chemistry program coupled with novel, high-throughput mass spectrometry-based screening methods. As the pioneer of this aspect of RNA-based drug discovery, Ibis scientists have filed numerous patent applications on its technology over recent years. Already, some of these patents have issued, and the division is continuing to make meaningful progress.

ISIS' INTELLECTUAL PROPERTY POSITION GROWTH
(cumulative number of patents obtained by year)



With control of more than 900 issued patents worldwide, Isis' leadership position in RNA-based drug discovery and development is formidable. In the past four years the company has more than doubled the number of patents it holds, and continues to file new applications on its inventions.



Isis has created a broad intellectual property estate through scientific innovation and opportunistic consolidation of related intellectual property. In 2001 for example, Isis further fortified its control of antisense technology when it exclusively licensed Hybridon's antisense chemistry and delivery technology patents.

In generating value from its intellectual property, Isis pursues three primary goals:

PROTECT THE COMPANY'S TECHNOLOGY, DRUGS AND LEADERSHIP POSITION Isis' patent estate protects its inventions in RNA-based drug discovery and discourages competition, safeguarding the investment made by the company and its shareholders.

In antisense technology, Isis' intellectual property addresses the use of antisense inhibitors as drugs and as functional genomics tools. It also covers antisense chemistries,

and drug discovery programs, and reward Isis and its shareholders for their investment in innovation.

ENCOURAGE RELATIONSHIPS THAT RESULT IN ADDITIONAL ANTISENSE DRUGS Isis' strategy is to expand its pipeline as broadly as possible by granting partners limited access to antisense technology. In drug discovery and/or development collaborations, Isis exchanges access to intellectual property and expertise for partial ownership in either a drug and/or the collaborating company. Antisense Therapeutics Limited and OncoGenex Technologies Inc. are examples of how Isis is providing access to antisense technology to newly established companies and in international capital markets.

In 2001, the company entered into several antisense drug discovery alliances with industry leaders that served this purpose, such as with

"OUR INNOVATION INCLUDES STATE-OF-THE-ART PROPRIETARY MANUFACTURING METHODS THAT FURTHER STRENGTHEN OUR LEADERSHIP POSITION."



DOUGLAS L. COLE, PH.D.
ISIS VICE PRESIDENT, DEVELOPMENT
CHEMISTRY AND PHARMACEUTICS

PATENT STRENGTH

inhibitor motifs, methods of using RNA/DNA oligonucleotides, antisense mechanisms of action, antisense manufacturing and methods of using genes. Ibis Therapeutics™ pioneering research has further strengthened the company's overall RNA intellectual property estate. Ibis has broadly filed patents on its technology, and has received several patents surrounding comparative genomic algorithms and other drug discovery inventions.

Isis actively defends its patent estate, particularly in the area of functional genomics. The company is in litigation with one provider of antisense reagents for infringement of its patents. Isis has notified many other companies who are using antisense as a functional genomics tool of its desire to collaborate. Such licensing collaborations provide partners with access to Isis patents necessary to support their internal antisense-based functional genomics

Eli Lilly and Company and Amgen. Isis granted these partners access to its proprietary second-generation chemistry and expertise in antisense research. These transactions were important to Isis as they reflected increased industry commitment to the discovery and development of antisense drugs.

GENERATE NEAR-TERM REVENUE THROUGH PATENT LICENSING Intellectual property licensing partnerships provide an additional source of revenue for the company. These relationships facilitate increased industry exposure to Isis' RNA-based drug discovery technologies. Licensing partnerships can range from antisense and Ibis drug discovery alliances, to GeneTrove™ functional genomics collaborations and to non-antisense patent licenses for drug discovery. Intellectual property licensing is a component of virtually every collaborative relationship Isis enters. It

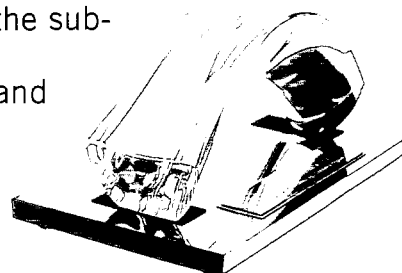
can also be the focus of a transaction, as in the case of Eyetech Pharmaceuticals, Inc. In a multi-million dollar transaction in 2001, Isis licensed specific chemistry patents to Eyetech for non-antisense compounds.

The reach and opportunity for licensing partnerships extend beyond antisense. Isis has non-antisense patents that have contributed revenue to the company, including patents on chemistries used in diagnostics and novel immunogenicity applications of oligonucleotide inhibitors.

Isis' patent estate is a very valuable asset, as it protects the investment made in pioneering and developing its technologies and drugs and generates revenue. Isis will continue its efforts to strengthen the company's patent estate.



Isis is honored to be the recipient of the seventh annual Helix Award, the highest acknowledgement of corporate excellence in the international biotechnology industry. This award is based on leadership in three distinct areas: scientific innovation, company growth and corporate citizenship. The Helix Award is presented by the Long Island Life Sciences Initiative and is jointly sponsored by BIO, Stony Brook University and The Center for Biotechnology. An independent panel of judges reviewed the submissions from nominated companies and KPMG LLP, an international professional services firm, tabulated the results.



NEW RELATIONSHIPS EXPAND THE APPLICATION OF ANTISENSE TECHNOLOGY



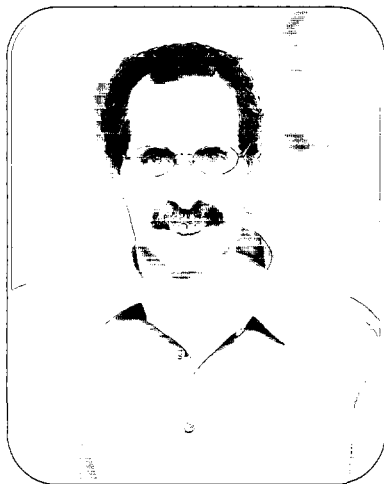
GROWING PIPELINE

IBIS THERAPEUTICS MILESTONES AND INNOVATION

TRANSFORMATION OF ANTISENSE TECHNOLOGY INTO A NEAR-TERM VALUE OPPORTUNITY



"IN ADDITION TO IMPROVED POTENCY AND SAFETY, OUR NEW GENERATION OF DRUGS OFFERS INCREASED PATIENT CONVENIENCE THROUGH LESS FREQUENT DOSING AND THE POTENTIAL FOR ORAL DELIVERY."



ARTHUR A. LEVIN, PH.D.
ISIS VICE PRESIDENT, TOXICOLOGY
AND PHARMACOKINETICS

INDUSTRY LEADERSHIP

"ISIS EMPLOYEES ARE INDUSTRY-LEADING SCIENTISTS. APPROXIMATELY 40% OF OUR EMPLOYEES HOLD A MASTERS, M.D. AND/OR PH.D. DEGREE."

In 1989, Isis set out to test and develop its technologies and use them to bring a stream of important new drugs to market. Today, the company is realizing its broad vision of establishing RNA-based drug discovery as a new sector of the pharmaceutical industry.

The company possesses the assets of a true technology leader:

- a large and exciting pipeline of products
- a strategic and powerful set of drug discovery engines in antisense research, GeneTrove™ and Ibis Therapeutics™
- a strong intellectual property position and sought-after core expertise
- a successful business strategy to achieve its goals
- an experienced management team and world-class scientists.



PATRICIA LOWENSTAM
ISIS VICE PRESIDENT, HUMAN RESOURCES
AND OPERATIONS

BOARD OF DIRECTORS

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President, GeneTrove™ a division of
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**"OUR INVESTMENT THESIS IS BASED
ON A SOLID BUSINESS PLAN THAT
LEVERAGES OUR PIPELINE, PROPRI-
ETARY TECHNOLOGY AND LEADING
INNOVATION TO CREATE VALUE."**



KAREN LUNDSTEDT
ISIS VICE PRESIDENT,
CORPORATE COMMUNICATIONS

This annual report contains forward-looking statements regarding the company's business and the therapeutic and commercial potential of its technologies and products in development. Any statement describing a goal, expectation, intention or belief of the company is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation activities and the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this annual report. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in Isis' Annual Report on Form 10-K for the year ended December 31, 2001, which accompanies this annual report and is on file with the U.S. Securities and Exchange Commission. As a result, the reader is cautioned not to rely on these forward-looking statements.

GeneTrove™ and Ibis Therapeutics™ are trademarks of Isis Pharmaceuticals, Inc. Vitravene® is a registered trademark of Novartis AG.

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NASDAQ: ISIS

ACKNOWLEDGMENTS

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FINANCIAL STRENGTH



GROUND-BREAKING RESEARCH



FORMIDABLE PATENT ESTATE



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